Computer and Information Science
Complex systems

Modeling and Simulation of Latent Tuberculosis

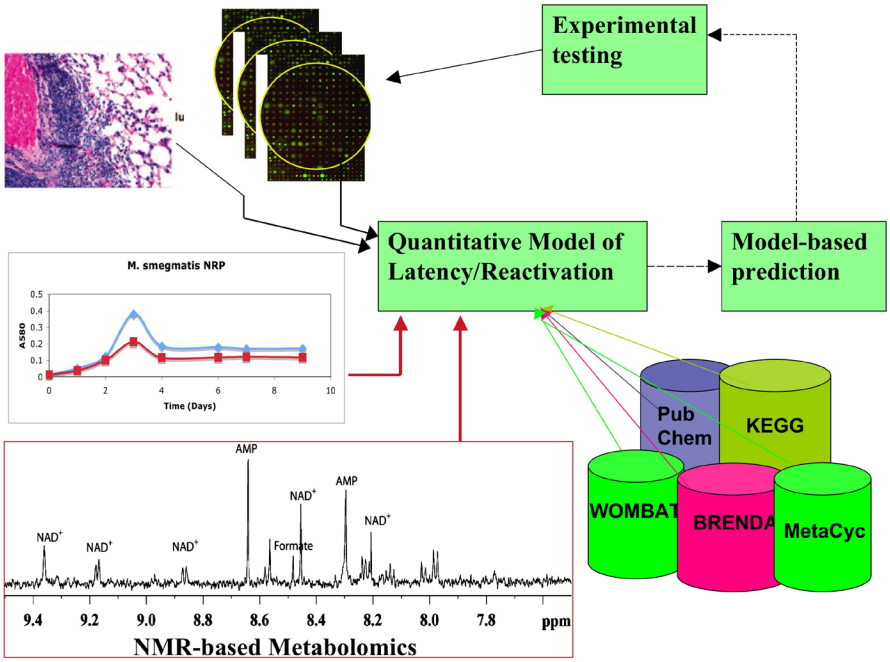

Figure 1: In order to develop predictive, multiscale models of host-Mtb interactions during disease and subsequent latency/ reactivation, scientists are integrating quantitative, multi-type immunopathogenesis data (e.g., genomic, metabolomic, and pathogen growth dynamics during latency) with public bioinformatics data resources (e.g., MetaCyc and KEGG warehouse information on biochemical pathways, BRENDA is an enzyme kinetics repository, and PubChem and WOMBAT are useful for obtaining chemical informatics data). The nuclear magnetic resonance (NMR)-based metabolomic data was obtained by T. Alam at Sandia.

Circuit-based framework is used to predict the response of the tubercle bacilli to hostile environmental conditions

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According to the 2008 World Health Organization's report, tuberculosis (TB), caused by the bacterium *Mycobacterium tuberculosis* (Mtb), continues to be a major international cause of illness and death worldwide. Mtb is able to persist in host tissues in a non-replicating persistent (NRP) or latent state. During latency, Mtb is present in the host, but does not produce any overt symptoms; this presents a challenge in the treatment of latent TB. With an estimated one third of the world's population carrying latent TB, reactivation of this highly contagious disease is of great concern, particularly in individuals with weakened immune systems. With nearly four thousand genes and over nine hundred reactions in its reconstructed metabolic network, the identification of which combination of genes and biochemical pathways constitute the "Achilles Heel" of Mtb is a non-trivial task. By coupling advances in high-throughput transcriptomics and metabolimics with large-scale computing, simulation, analysis, and optimization tools, scientists are meeting this challenge. As in other science and engineering fields, modeling and simulation is serving as a transformative bridge in understanding the multiscale phenomena of latency and reactivation in tuberculosis.

Through a five-year grant award from the National Institutes of Health, researchers at Sandia are partnering with the University of New Mexico and Los Alamos National Laboratory to develop models that enable a quantitative understanding of the genetic basis of latency and reactivation in a murine model of tuberculosis. The larger goal of this collaborative effort is to leverage the large-scale biological network simulator BioXyce, based on Sandia's parallel electronic circuit simulation tool Xyce™ , to understand the response of Mtb within the microenvironment of a granuloma, which is an aggregation of host immune cells that function to cooperatively quarantine but not completely eliminate the mycobacterium.

Understanding the genetic and biochemical mechanisms Mtb employs to persist within the hostile environment of the granuloma will help identify viable chemotherapies to treat the extremely large number of individuals with latent tuberculosis.

Using the Wayne model of hypoxic (oxygen poor) NRP, scientists are generating multi-scale, high time resolution dynamic profiles of the system in order to produce a high fidelity, predictive quantitative model of Mtb response to varying environmental conditions (Figure 1). *In vitro* studies of Mtb in a hypoxic microenvironment suggest that the tubercle bacilli can circumvent the shortage of oxygen by developing alternative energy generation mechanisms by way of the glyoxylate bypass pathway (Figure 2). BioXyce models of this important pathway have been constructed and simulations in the absence and presence of various inhibitory molecules have been conducted (Figure 2). Rather than probing the singular effect of a small molecule on a target protein, a large-scale circuit simulation framework enables researchers to probe in parallel the ripple effect a single molecule or group of small-molecules has on the entire system. This approach, coined "systems chemical biology", is being used to identify small molecules that directly or indirectly interfere with latency-related pathways (Figure 2). As advances in biotechnology propel science deeper into the "omics" age, large-scale simulation is quickly becoming the enabling link that transforms biological data into scientific discoveries in the medical, environmental, and energy sciences.

References

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2. E. May, R. Schiek, BioXyce: An engineering platform for the study of cellular systems. *IET Systems Biology Journal*, **3**(2):77-89, March 2009.

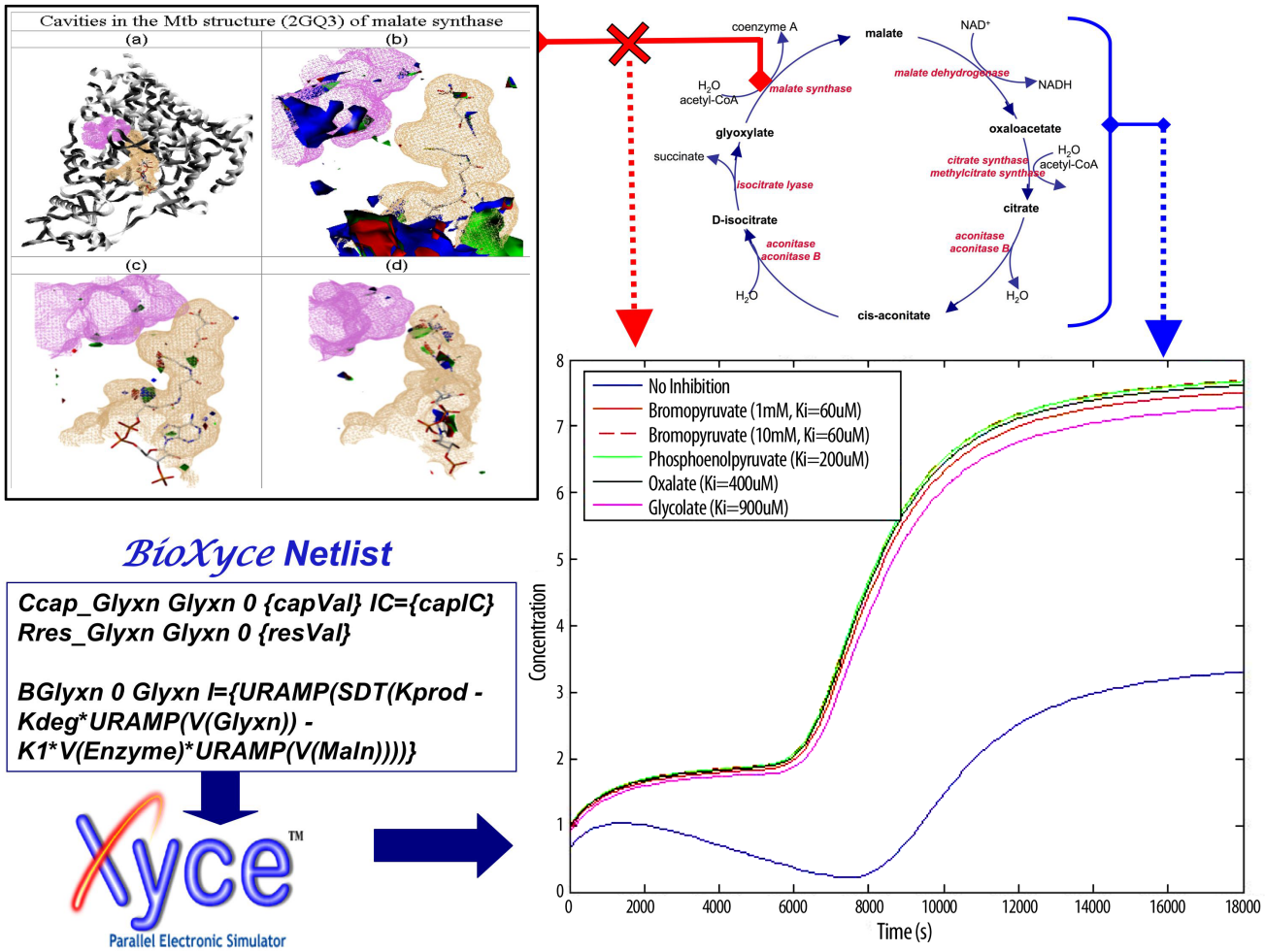

Figure 2: Simulation of the glyoxylate pathway in the presence and absence of inhibitory molecules (figure of small molecule interaction with malate synthase courtesy of Oprea Lab, UNM-HSC Biocomputing Division; pathway recreated from BioCyc, www.biocyc.org).

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